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# Dimethoxypyrimidines as Novel Herbicides. Part 1. Synthesis and Herbicidal Activity of Dimethoxyphenoxyphenoxypyrimidines and Analogues*

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**Abstract:** A number of 6-(4-phenoxyphenoxy)pyrimidines and triazines were synthesized and their herbicidal activity was measured. Compounds with the methoxy groups at the 2- and 4-positions on the pyrimidine and triazine rings exhibited high herbicidal activity. Introduction of a substituent into the 5-position of the pyrimidine ring diminished the activity. In the phenoxyphenoxy substructure at the 6-position, the central ether bond can be replaced by a methylene group without loss of activity. The optimum substituent on the terminal phenyl ring was 3-trifluoromethyl. The compounds showed a strong Hill reaction inhibition, but unfortunately showed poor selectivity between weeds and crops.

Key words: phenoxyphenoxypyrimidines, phenoxyphenoxy-*s*-triazines, Hill reaction inhibitors, 2,6-dimethoxy-4-[4-(3-trifluoromethylphenoxy)phenoxy]-pyrimidine, 2,6-dimethoxy-4-[4-(3-trifluoromethylphenoxy)phenoxy]-*s*-triazine, herbicides.

## 1 INTRODUCTION

One approach to obtaining a new herbicide with a 'novel' structure is to make more or less drastic modifications in structures of known herbicides as models. Our first attempts at the synthesis of new herbicides incorporating a dimethoxypyrimidine moiety started with structural modifications of sulfonylurea herbicides such as chlorsulfuron (Fig. 1; **1**) at their nitrogen-heterocyclic sites, because the sulfonylureas are highly active at very low rates.[1]

Among the compounds synthesized was a sulfonylurea (**2**) substituted by a phenoxyphenoxy structure. The sulfonylurea itself (**2**) showed no herbicidal activity, but surprisingly the phenoxyphenoxytriazine (**3a**), one of the building blocks of the sulfonylurea (**2**), showed post-emergent herbicidal activity at 1 kg ha$^{-1}$ against broadleaf weeds such as *Polygonum nodosum*, *Amaranthus retroflexus* L., *Chenopodium album* L. and *Cyperus iria* L. This led to an investigation of the substituted phenoxyphenoxytriazines and their *N*-heteroaromatic analogues based on the phenoxyphenoxytriazine (**3a**) as the primary lead structure. Single phenoxy-substituted triazines and pyrimidines have been reported to show pre-emergent herbicidal activity,[2] but the phenoxyphenoxy analogues are unknown. This paper describes the synthesis and post-emergent herbicidal activity of a series of phenoxyphenoxytriazines and -pyrimidines (Fig. 2).

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## 2 MATERIALS AND METHODS

### 2.1 Instrumental analysis

All melting points were uncorrected. IR spectra were measured on a Hitachi Infrared spectrophotometer using potassium bromide disc and sodium chloride



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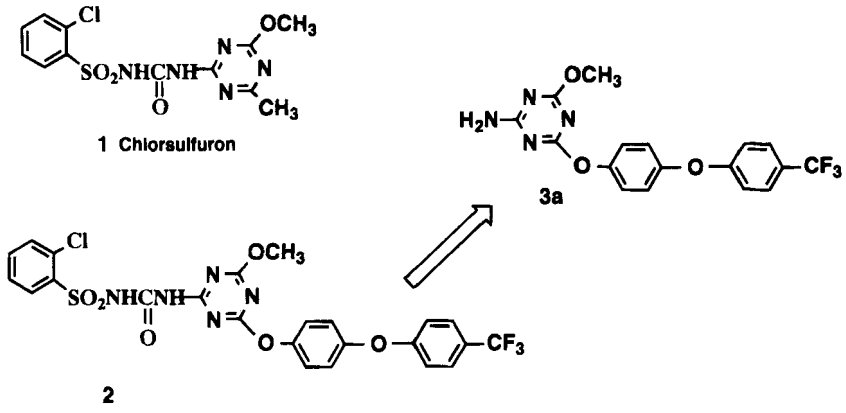



Fig. 1. Prototype compounds of the phenoxyphenoxypyrimidine herbicides.

liquid film cell. [$^1$H]NMR spectra were recorded on a JNM-PMX60 NMR spectrometer at 60 MHz using tetramethylsilane (TMS) as an internal standard.

## 2.2 Preparation of materials

*2.2.1 Syntheses of triazine derivatives*

Phenoxyphenoxy triazine derivatives were prepared as outlined in Fig. 3. 2-Amino- and 2-alkylamino-4,6-dichloro-1,3,5-triazine (**4**) obtained from trichloro-1,3,5-triazines (**6**) with ammonia and alkylamines were reacted with sodium methoxide or sodium methanethiolate and then with the salts of 4-(4-trifluoromethylphenoxy)phenol (Route A). The trichlorotriazines (**6**) were also treated directly with the methoxide and subsequently substituted phenoxyphenols (**8**) under similar conditions (Route B). The compounds **3a–3f** were prepared by Route A and compounds **9a–9i** by Route B.

*2.2.2 Syntheses of pyrimidine derivatives*

Most of the phenoxyphenoxy pyrimidines (compounds **12a–12t**, **12z** and **17**) were prepared from either the 4-chloro- (**10**), the 4,6-dichloro- (**13**) or the 2-chloropyrimidines (**16**) by treatment with 4-substituted phenols (**11**: Y = O and **14**) in the presence of a base as outlined in Fig. 4 (Route C). Some 2-methoxy- and 2-methylamino pyrimidines (compounds **21a–21k**) with a variety of substituents at the 4-position were prepared by reacting either the 2-methane- or 2-benzyl-sulfonyl pyrimidines (**20**) with sodium alkoxides and methylamine as shown in Fig. 5 (Route D).[3]

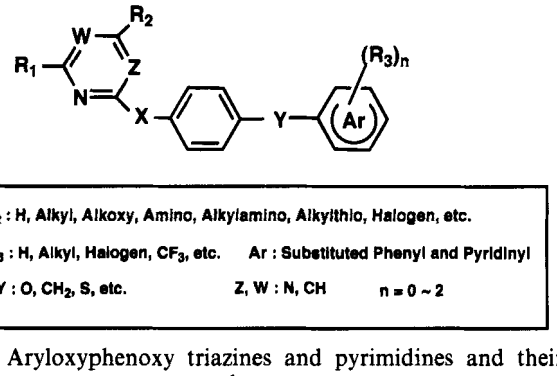



Fig. 2. Aryloxyphenoxy triazines and pyrimidines and their analogues.

Phenoxyphenoxy pyrimidine analogues, in which the terminal phenyl ring was replaced by a pyridine ring (compounds **12'a–12'c**), and the ether bridge was absent (compound **12u**) or replaced by $OCH_2$, $CH_2$, $C(CH_3)_2$ and NH (compounds **12v–12y**), were prepared via Route C as outlined in Fig. 4.

The pyridyl compound (**25**) was prepared by reducing the dichlorophenoxypyridine (**24**) obtained via the dichlorodimethoxypyridine (**23**) from 2,4,6-trifluoro-3,5-dichloropyridine (**22**) as shown Fig. 5 (Route E).

The phenoxyphenyl (**28**), phenoxyphenoxymethyl (**31**) and phenoxybenzyl (**36**, **37**) compounds were prepared as outlined in Figs 6 and 7 (Routes F, G and H). Compound **34** with the phenoxybenzyl substituent was prepared by reacting *O*-methylisourea (**33**) with ethyl phenoxyphenylacetoacetate (**32**).

Most of the final compounds were obtained as pasty oils, while some were isolated as crystals which were purified by column chromatography on silica gel (Wakogel C-300, Wako Pure Chemical Industries, Ltd, Osaka, Japan). Melting points (m.p.) and refractive indices ($n_D^{20}$) of compounds are shown in Tables 1–5 below.

*2.2.3 Syntheses of typical compounds*

*2.2.3.1 2-Amino-4-methoxy-6-[4-(4-trifluoromethylphenoxy)phenoxy]-1,3,5-triazine (3a: $R_1 = NH_2$, $R_2 = OCH_3$, Fig. 3).* 28% Sodium methoxide (20 g, 0·1 mol) was added dropwise to a solution of 2-amino-4,6-dichloro-1,3,5-triazine[4] (**4**: $R_1 = NH_2$; 16·5 g, 0·1 mol) in methanol (200 ml) with stirring at 0°C. The mixture was allowed to warm to room temperature and stirred for 5 h, then poured into ice water. The precipitate was filtered, washed with water and dried to obtain 2-amino-4-chloro-6-methoxy-1,3,5-triazine (**5**: $R_1 = NH_2$, $R_2 = OCH_3$, yield: 12 g, 75%).

4-(4-Trifluoromethylphenoxy)phenol (3·6 g, 14·2 mmol) in *N*,*N*-dimethylformamide (DMF; 10 ml) was

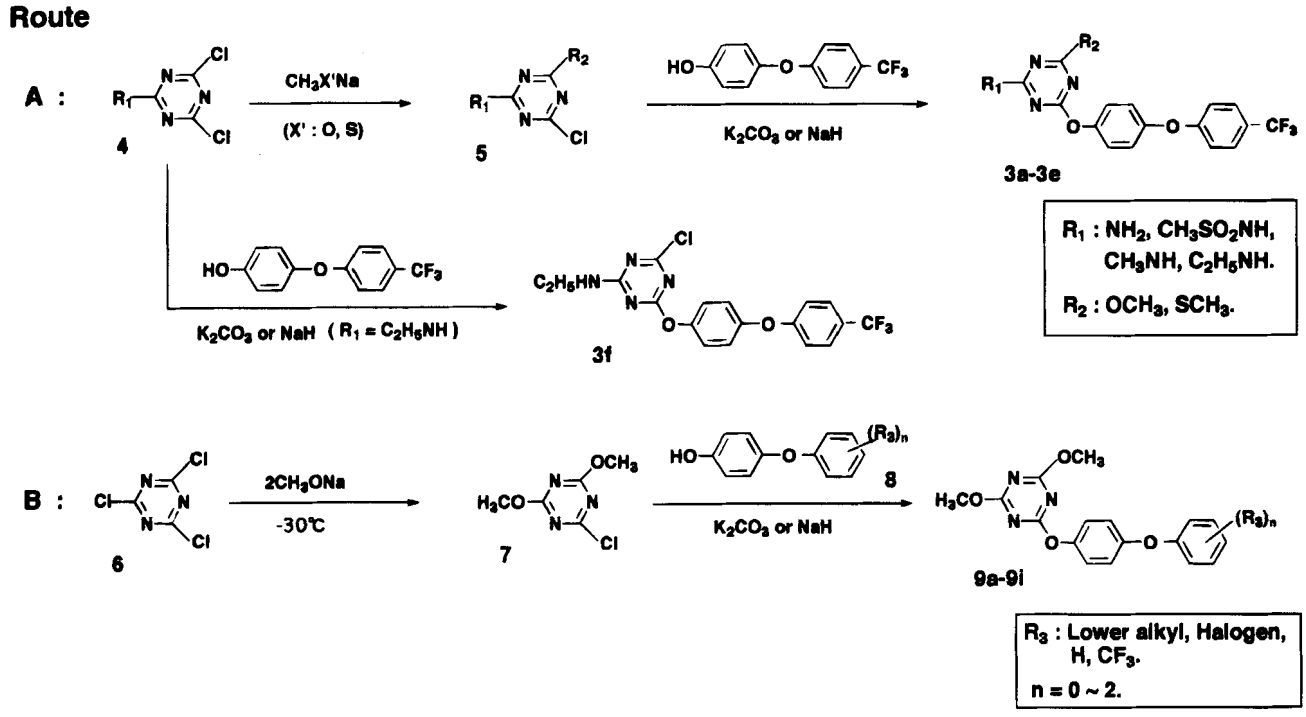



Fig. 3. Synthetic routes for the phenoxyphenoxy triazines.

added dropwise to a suspension of 60% sodium hydride (0·6 g, 15 mmol) in DMF (30 ml) with stirring at 15–20°C. After stirring at room temperature for 15 min, 2-amino-4-chloro-6-methoxy-1,3,5-triazine (**5**: 2·2 g, 13·7 mmol) in DMF (10 ml) was added dropwise to the mixture at room temperature, which was stirred at 60°C for another 4 h. The mixture was poured into ice water and extracted with ethyl acetate (2 × 30 ml). The extract was washed with water, dried with magnesium sulfate, and then evaporated. A small portion of ethanol and *n*-hexane was added to the residue, the precipitated solids were collected and washed with cold ethanol to give compound **3a** as colourless crystals, m.p. 125–137°C. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 3·87

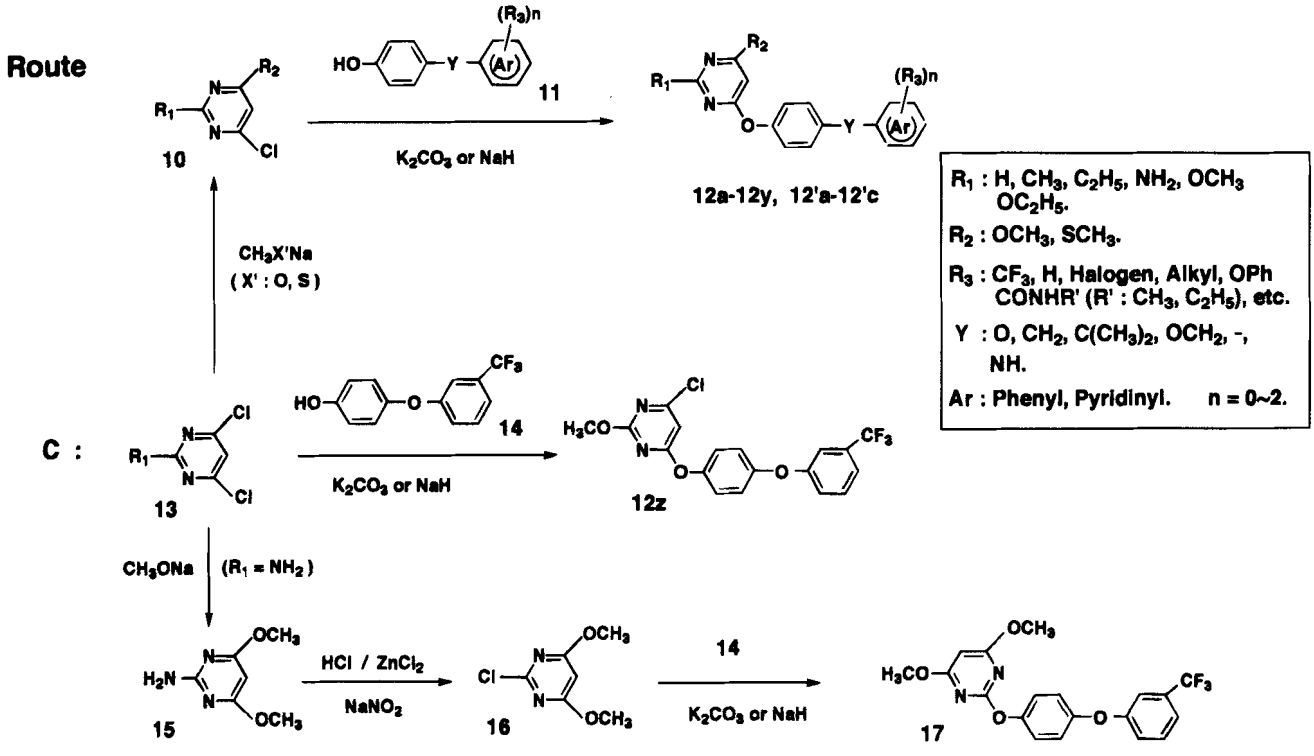



Fig. 4. Synthetic routes for the phenoxyphenoxy pyrimidines and analogues.

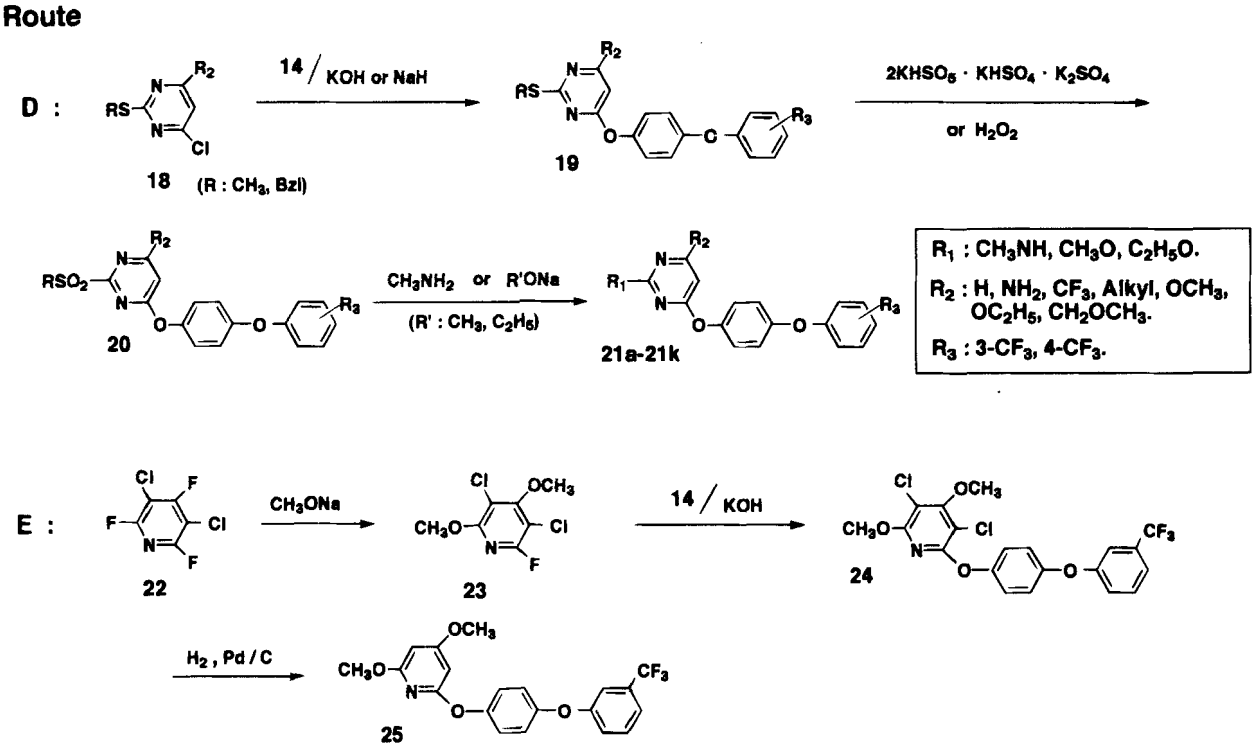



Fig. 5. Synthetic routes for the phenoxyphenoxy pyrimidines and pyridine. (Bzl ≡ benzyl).

(3H, s, $OCH_3$), 5·67 (2H, broad, $NH_2$), 6·93–7·60 (8H, m, Ar-H), yield: 3·9 g (76%).

*2.2.3.2 2-Methylamino-4-methoxy-6-[4-(3-trifluoromethylphenoxy)phenoxy] pyrimidine* (***21k***: $R_1 = CH_3NH$, $R_2 = OCH_3$, $R_2 = 3\text{-}CF_3$, *Fig. 5*). To a solution of 4-methoxy-2-methylthio-6-[4-(3-trifluoromethylphenoxy)phenoxy]pyrimidine (**19**: R = $CH_3$, $R_2$ = $OCH_3$, $R_3$ = 3-$CF_3$; 3·6 g, 8 mmol) in methanol (50 ml), oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; 7·1 g) in water (50 ml) was added. After stirring at room temperature for 3 h, the mixture was poured into water. The separated crystals were collected and recrystallized from methanol to give the methanesulfonyl compound (**20**: R = $CH_3$, $R_2$ = $OCH_3$, $R_3$ = 3-$CF_3$) as colourless crystals, m.p. 102–105°C, yield: 2·6 g (67·0%).

To a mixture of **20** (3·5 g, 8 mmol) in acetonitrile (50 ml), a 40% aqueous solution of methylamine (0·7 g, 9 mmol) was added at room temperature. After stirring at room temperature for 30 min, the mixture was poured into water. The separated crystals were collected and recrystallized from methanol to give compound **21k** as colourless crystals, m.p. 98–100°C. [$^1$H]NMR (carbon tetrachloride) $\delta$ ppm: 2·90 (3H, d, $NHCH_3$), 3·87 (3H, s, $OCH_3$), 5·20 (1H, broad, $NH$), 5·35 (1H, s,

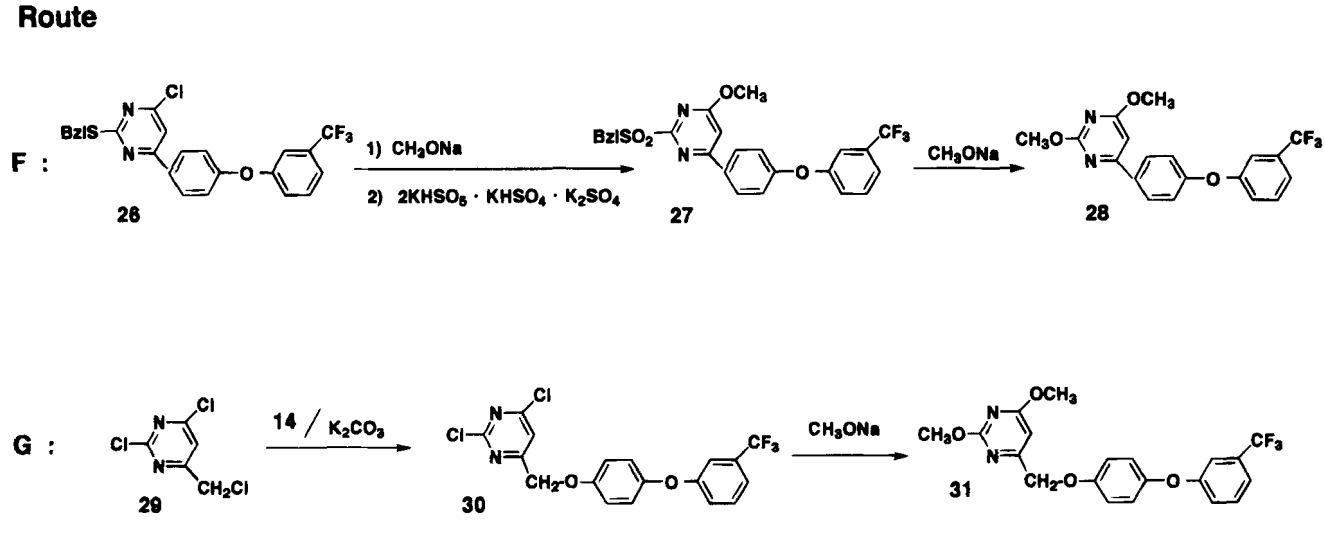



Fig. 6. Synthetic routes for the phenoxyphenoxymethyl pyrimidines.

**Route**

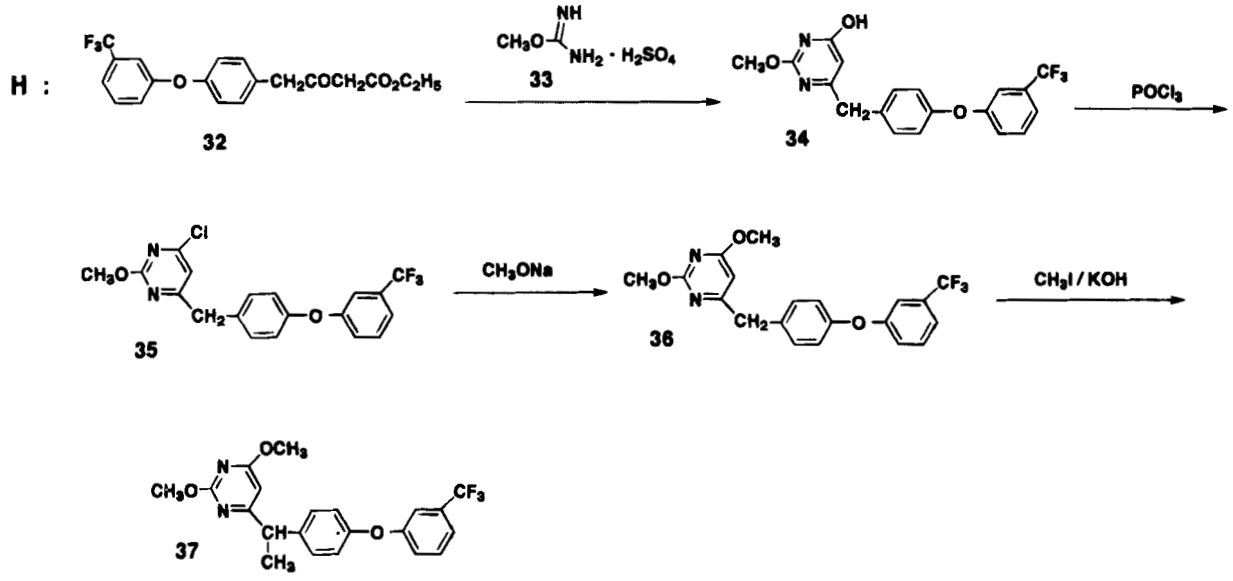



**Fig. 7.** Synthetic route for the phenoxybenzyl pyrimidines.

*CH*), 6·8–7·6 (8H, m, Ar-H), IR $\nu$ cm$^{-1}$: 3270 (NH), 1620 (C=N), yield: 2·2 g (73·3%).

*2.2.3.3 2,4-Dimethoxy-6-[4-(3-trifluoromethylphenoxy)phenoxy]pyridine* **25** (*Fig. 5*). To 3,5-dichloro-2,4,6-trifluoropyridine (**22**: 15 g, 74·3 mmol) in methanol (500 ml) 28% sodium methoxide (30 g, 156 mmol) was added dropwise at 10°C for 30 min. The mixture was stirred at 25°C for 1 h, then poured into water and extracted with ethyl acetate. The extract was evaporated to give the product (**23**)[5] as a powder, m.p. 66–68°C. [$^1$H]NMR (deuterochloroform) $\delta$ ppm: 3·99 (3H, s, $OCH_3$), 4·04 (3H, s, $OCH_3$), yield: 14·3 g (85·2%).

To a mixture of 4-(3-trifluoromethylphenoxy)phenol (**14**: 1·7 g, 6·6 mmol) and potassium hydroxide (0·64 g, 11·4 mmol) in DMF (30 ml), the pyridine (**23**: 1·5 g, 6·6 mmol) prepared above was added at room temperature. After stirring for 1 h, the solution was poured into ice/water and extracted with ethyl acetate. The extract was evaporated to give a pasty oil of the phenoxyphenoxy pyridine (**24**), $n_D^{20}$ = 1·5586. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 3·67 (3H, s, $OCH_3$), 4·00 (3H, s, $OCH_3$), 7·08–7·30 (8H, m, Ar-H), yield: 2·3 g (78·2%).

A mixture of **24** (5·0 g, 10·9 mmol), potassium carbonate (4·5 g, 32·6 mmol) and 10% Pd-C (1 g) in ethanol (150 ml) was stirred under hydrogen at room temperature for 5 h. After filtering the mixture, the filtrate was evaporated and the residue extracted into ethyl acetate. The extract was dried with sodium sulfate and evaporated. The residual oil was purified by column chromatography over silica gel using *n*-hexane + ethyl acetate (20 + 1 by volume) as eluent to give compound **25** as a colourless pasty oil, $n_D^{20}$ = 1·5491. [$^1$H]NMR (deuterochloroform) $\delta$ ppm: 3·80 (6H, s, $OCH_3$), 5·90 (2H, s, *CH*), 7·01–7·48 (8H, m, Ar-H), IR $\nu$ cm$^{-1}$: 1610 (C=N), 1210 (—O—Ph), yield: 3·4 g (80.8%).

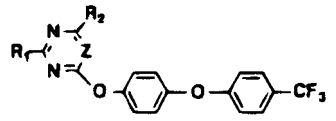
*2.2.3.4 2,4-Dimethoxy-6-[4-(3-trifluoromethylphenoxy)]phenylpyrimidine* **28** (*Fig. 6*). Following the synthetic method for compound **21k** described above, the benzylsulfonylpyrimidine (**27**: 3 g, 6 mmol) was prepared and allowed to react with sodium methoxide (0·3 g, 6 mmol) to give compound **28** as colourless crystals, m.p. 71–74°C. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 4·00 (3H, s, $OCH_3$), 4·05 (3H, s, $OCH_3$), 6·70 (1H, s, *CH*), 7·05–8·10 (8H, m, Ar-H), yield: 1·5 g (66·4%).

*2.2.3.5 2,4-Dimethoxy-6-[4-(trifluoromethylphenoxy)phenoxy]methylpyrimidine* **31** (*Fig. 6*). To a suspension of 4-(3-trifluoromethylphenoxy)phenol (**14**: 3·8 g, 15 mmol) and potassium carbonate (2·3 g, 16·5 mmol) in acetone (100 ml), 2,4-dichloro-6-chloromethylpyrimidine[6] (**29**: 3·3 g, 16·7 mmol) was added at room temperature. The mixture was stirred at 20°C for 4 h, poured into water and extracted with ethyl acetate. The extract was evaporated to give the product as a powder (**30**: 6·0 g, 96·8%). The crude dichloropyrimidine was used without further purification.

To a solution of the dichloropyrimidine (**30**: 6·2 g, 15 mmol) in methanol (50 ml), 28% sodium methoxide (6·2 g, 30 mmol) was added at 10°C and heated under reflux for 3 h, then poured into water and extracted with ethyl acetate. The extract was dried with sodium sulfate and evaporated. The residual oil was purified by column chromatography, eluting with ethyl acetate + *n*-hexane (1 + 5 by volume) to give compound **31**

**TABLE 1**

Structures, Physical Properties and Post-emergence Herbicidal Activities of 4-Trifluoromethylphenoxyphenoxy-pyrimidines and Triazines



| No. | $R_1$ | $R_2$ | Z | m.p. or $n_D^{20}$ | Herbicidal activity[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ech | Dig | Pol | Ama | Che | Cyp |
| **3a** | $NH_2$ | $OCH_3$ | N | 125–137°C | 1 | 1 | 5 | 5 | 3 | 5 |
| **3b** | $CH_3SO_2NH$ | $OCH_3$ | N | 1·5421 | 1 | 1 | 4 | 5 | 5 | 5 |
| **3c** | $CH_3NH$ | $OCH_3$ | N | 159–162°C | 0 | 0 | 1 | 0 | 1 | 0 |
| **3d** | $C_2H_5NH$ | $OCH_3$ | N | 146–149°C | 0 | 0 | 0 | 0 | 0 | 0 |
| **3e** | $C_2H_5NH$ | $SCH_3$ | N | 136–138°C | 0 | 0 | 0 | 0 | 0 | 0 |
| **3f** | $C_2H_5NH$ | Cl | N | 131–133°C | 0 | 0 | 0 | 0 | 0 | 0 |
| **9a** | $OCH_3$ | $OCH_3$ | N | 1·5327 | 3 | 3 | 4 | 5 | 5 | 5 |
| **12a** | $NH_2$ | $OCH_3$ | CH | 79–82°C | 1 | 1 | 1 | 1 | 0 | 1 |
| **12b** | $OCH_3$ | $OCH_3$ | CH | 65–68°C | 0 | 0 | 1 | 1 | 4 | 0 |
| **12c** | H | $OCH_3$ | CH | 89–93°C | 0 | 0 | 0 | 0 | 0 | 0 |
| **21a** | $OCH_3$ | $NH_2$ | CH | 155–158°C | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Herbicidal activity was evaluated at a rate of 1 kg AI $ha^{-1}$.
[b] Ech: *Echinochloa crus-galli.* Dig: *Digitaria adscendens.* Pol: *Polygonum nodosum.* Ama: *Amaranthus retroflexus.* Che: *Chenopodium album.* Cyp: *Cyperus iria.*

as a yellow pasty oil, $n_D^{20} = 1·5482$. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 4·00 (3H, s, $OCH_3$), 4·05 (3H, s, $OCH_3$), 5·05 (2H, s, $CH_2O$), 6·65 (1H, s, *CH*), 7·00–7·50 (8H, m, Ar-H), yield: 3·8 g (62·3%).

*2.2.3.6 4-Hydroxy-2-methoxy-6-[4-(3-trifluoromethylphenoxy)benzyl]pyrimidine* **34** (*Fig.* 7). To a mixture of ethyl 4-[4-(3-trifluoromethylphenoxy)phenyl]-3-oxobutyrate (**32**: 31·3 g, 85·4 mmol) and sodium hydroxide (10·3 g, 258 mmol) in water (60 ml), *O*-methylisourea hydrogen sulfate (**33**: 14·8 g, 86 mmol) was added. After stirring at room temperature for 24 h, the mixture was poured into water and washed with ether (200 ml). To the aqueous layer, a 5% solution of hydrochloric acid was added dropwise until the pH was 2–3. After extracting with chloroform, the extract was washed with water and dried. After removal of chloroform, the residue was recrystallized from methanol to give the product **34** as colourless crystals, m.p. 167–170°C. Yield, 5·6 g (17·4%).

*2.2.3.7 2,4-Dimethoxy-6-[4-(3-trifluoromethylphenoxy)benzyl]pyrimidine* **36** (*Fig.* 7). The 4-hydroxypyrimidine (**34**: 5·5 g, 14·6 mmol) prepared as described above, was added to phosphorus oxychloride (25 ml). After stirring at room temperature for 2 h, the unreacted phosphorus oxychloride was removed under vacuum. Ice/water was added to the residue and the mixture extracted with ether (200 ml). The extract was washed with water and dried with sodium sulfate. After evaporation, the residual oil was purified by column chromatography eluting with *n*-hexane + ethyl acetate (5 + 1 by volume) to give the 4-chloropyrimidine (**35**) as a colourless pasty oil. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 3·95 (2H, s, $CH_2$), 4·00 (3H, s, $OCH_3$), 6·70 (1H, s, *CH*), 6·9–7·4 (8H, m, Ar-H), IR $\nu$ $cm^{-1}$: 1560 (C=N), 1240 (—O—Ph), yield: 4·5 g (78·0%).

To a solution of the 4-chloropyrimidine (**35**: 3·0 g, 7·6 mmol) in methanol (50 ml), a solution of 28% sodium methoxide (1·5 g, 27·8 mmol) was added dropwise. After stirring at 50–55°C for 4 h, the mixture was evaporated to remove methanol and extracted with ether (200 ml). The extract was washed with water, dried and evaporated. The residual oil was purified by column chromatography eluting with *n*-hexane + ethyl acette (15 + 1 by volume) to give compound **36** as a pale yellow pasty oil, $n_D^{20} = 1·5471$. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 3·95 (2H, s, $CH_2$), 4·0 (6H, s, $OCH_3$), 6·2 (1H, s, *CH*), 6·9–7·4 (8H, m, Ar-H), IR $\nu$ $cm^{-1}$: 1600 (C=N), 1240 (—O—Ph), yield: 2·3 g (77·4%).

*2.2.3.8 2,4-Dimethoxy-6-{1-[4-(3-trifluoromethylphenoxy)phenyl]ethyl}pyrimidine* **37** (*Fig.* 7). To a mixture of compound **36** (1·5 g, 3·8 mmol) and potassium hydroxide (0·6 g, 12·5 mmol) in DMF (50 ml), methyl iodide (4·0 g, 28·2 mmol) was added at room temperature. The mixture was stirred for 24 h, then poured into water and extracted with benzene. The extract was washed with water, dried and evaporated. The residue was purified by column chromatography eluting with ethyl acetate + *n*-hexane (1 + 5 by volume) to give compound **37** as a pasty oil, $n_D^{20} = 1·5320$. [$^1$H]NMR (deuterochloroform), $\delta$ ppm: 1·70 (3H, d, $CH_3$), 4·00 (7H, m, $OCH_3$, $CH_3$—*CH*), 6·2 (1H, s, *CH*), 6·85–7·60

(8H, m, Ar-H), IR $\nu$ $cm^{-1}$: 1600 (C=N), 2920 (CH), yield: 1·3 g (83·9%).

### 2.3 Biological tests

#### *2.3.1 Herbicidal test*

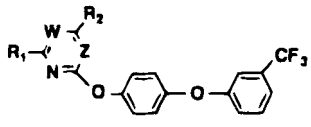
Plastic pots (surface area: 11 × 11 $cm^2$, depth: 11 cm) were filled with a clay loam soil (clay 16·9%, total carbon 1·0%, pH 6·6) and kept in a greenhouse (20–32°C). Watering was through holes located at the bottom of the pots. All of the pots were maintained adequately wet throughout the test periods. Post-emergence herbicidal activity was evaluated at 1 kg AI $ha^{-1}$ for each compound. The test plants were barnyardgrass (*Echinochloa crus-galli* (L.) Beauv.), southern crabgrass (*Digitaria adscendens* Henr.), smartweed (*Polygonum nodosum*), redroot pigweed (*Amaranthus retroflexus* L.), lambsquarters (*Chenopodium album* L.) and rice flatsedge (*Cyperus iria* L.).

For the post-emergence test, wettable powders were prepared by mixing the compound (10 g) 'Demol' N and 'Emulgen' 810 (surfactants; 0·5 + 0·5 g), 'Kunilite' 201 (diatomaceous earth; 24 g) and 'Dieclite' (clay; 65 g). Each compound, formulated as the wettable powder, was diluted with water to give a concentration of 1 g AI $litre^{-1}$, and the diluted suspension was sprayed over the foliage of the test plants at a volume of 1 litre $ha^{-1}$ and rate of 1 kg AI $ha^{-1}$. Spraying was performed two weeks after sowing the seeds and 11 days after germination. The plants were at either the one- or two-leaf stage. Approximately two weeks after spraying, the herbicidal activity of each compound was judged by visual observation of the treated plants in comparison with the untreated controls. The herbicidal activity was assessed on a scale of 0–5, where 5: greater than 90% growth inhibition, 4: 70 to 90% growth inhibition, 3: 40 to 70% growth inhibition, 2: 20 to 40% growth inhibition, 1: 5 to 20% growth inhibition, 0: growth inhibition of less than 5%. The activities presented in Tables 1–5 are herbicidal ratings against six weed species tested at 1 kg AI $ha^{-1}$ by the post-emergence tests.

For several compounds with prominent post-emergence activity, the activity was re-tested at 0·25 and 0·5 kg AI $ha^{-1}$ on a broad spectrum of grass and broadleaf species. Besides the six weed species listed above, other species, including crop plants, were examined: rice (*Oryza sativa* L.), wheat (*Triticum aestivum* L.),

**TABLE 2**

Structures, Physical Properties and Post-emergence Herbicidal Activities of 3-Trifluoromethylphenoxyphenoxy-pyrimidines, Triazines and Pyridines




| | | | | | | *Herbicidal activity*[a,b] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *No.* | $R_1$ | $R_2$ | *Z* | *W* | *m.p. or* $n_D^{20}$ | Ech | Dig | Pol | Ama | Che | Cyp | $pI_{50}$[c] |
| **25** | $OCH_3$ | $OCH_3$ | CH | CH | 1·5491 | 0 | 3 | 4 | 4 | 4 | 1 | 6·14 |
| **12d** | $OCH_3$ | $OCH_3$ | CH | N | 1·5350 | 5 | 5 | 5 | 5 | 5 | 5 | 7·35 |
| **9b** | $OCH_3$ | $OCH_3$ | N | N | 1·5389 | 5 | 5 | 5 | 5 | 5 | 5 | 7·49 |
| **17** | $OCH_3$ | $OCH_3$ | N | CH | 111–113°C | 0 | 0 | 0 | 0 | 0 | 0 | *[d] |
| **12z** | $OCH_3$ | Cl | CH | N | 1·5595 | 0 | 0 | 4 | 1 | 3 | 0 | 5·44 |
| **12e** | H | $OCH_3$ | CH | N | 1·5451 | 0 | 1 | 0 | 0 | 0 | 0 | * |
| **12f** | $CH_3$ | $OCH_3$ | CH | N | 1·5428 | 4 | 3 | 5 | 5 | 5 | 4 | * |
| **12g** | $C_2H_5$ | $OCH_3$ | CH | N | 1·5346 | 3 | 3 | 2 | 1 | 2 | 1 | * |
| **21b** | $OC_2H_5$ | $OCH_3$ | CH | N | 84–86°C | 1 | 0 | 1 | 1 | 2 | 0 | * |
| **21c** | $OCH_3$ | H | CH | N | 1·5532 | 0 | 0 | 0 | 1 | 1 | 0 | * |
| **21d** | $OCH_3$ | $CH_3$ | CH | N | 1·5445 | 4 | 3 | 5 | 5 | 5 | 4 | * |
| **21e** | $OCH_3$ | $C_2H_5$ | CH | N | 1·5418 | 1 | 2 | 2 | 5 | 3 | 0 | * |
| **21f** | $OCH_3$ | $C_3H_7$ | CH | N | 1·5355 | 0 | 0 | 0 | 0 | 0 | 0 | * |
| **21g** | $OCH_3$ | $OC_2H_5$ | CH | N | 1·5410 | 2 | 3 | 4 | 5 | 5 | 4 | * |
| **21h** | $OCH_3$ | $CH_2OCH_3$ | CH | N | 1·5415 | 1 | 4 | 4 | 5 | 5 | 3 | * |
| **21i** | $OCH_3$ | $CF_3$ | CH | N | 1·5147 | 0 | 0 | 0 | 0 | 0 | 0 | * |
| **12h** | $OCH_3$ | $SCH_3$ | CH | N | 1·5651 | 3 | 4 | 4 | 4 | 5 | 4 | * |
| **21j** | $OCH_3$ | $NH_2$ | CH | N | 115–118°C | 0 | 0 | 0 | 0 | 0 | 0 | * |
| **21k** | $NHCH_3$ | $OCH_3$ | CH | N | 98–100°C | 0 | 0 | 0 | 0 | 0 | 0 | * |

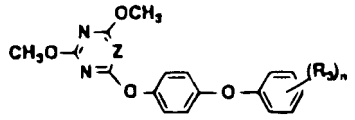
[a,b] As in Table 1.

[c] The Hill inhibitory activity is expressed as $pI_{50}$.

[d] * Not tested.

**TABLE 3**

Structures, Physical Properties and Post-emergence Herbicidal Activities of Phenoxyphenoxypyrimidines and Triazines

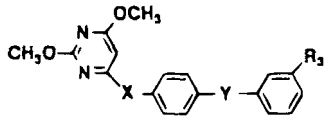


| No. | $(R_3)_n$ [n = 1, 2] | Z | m.p. or $n_D^{20}$ | Herbicidal activity[a,b] | | | | | | $pI_{50}$[c] | π |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Ech | Dig | Pol | Ama | Che | Cyp | | |
| **9c** | 2-$CF_3$ | N | 142–144°C | 0 | 0 | 0 | 0 | 0 | 0 | * | |
| **9b** | 3-$CF_3$ | N | 1·5389 | 5 | 5 | 5 | 5 | 5 | 5 | * | |
| **9a** | 4-$CF_3$ | N | 1·5327 | 3 | 3 | 4 | 5 | 5 | 5 | * | |
| **12d** | 3-$CF_3$ | CH | 1·5350 | 5 | 5 | 5 | 5 | 5 | 5 | 7·35 | 0·88 |
| **12i** | H | CH | 1·5759 | 4 | 4 | 5 | 5 | 5 | 4 | 6·90 | 0 |
| **12j** | 3-F | CH | 1·5695 | 4 | 5 | 5 | 5 | 5 | 4 | 7·15 | 0·14 |
| **12k** | 3-Cl | CH | 1·5920 | 4 | 5 | 5 | 5 | 5 | 4 | 7·18 | 0·71 |
| **12l** | 3-Br | CH | 1·5959 | 3 | 4 | 4 | 5 | 5 | 4 | 7·29 | 0·86 |
| **12m** | 3-$CH_3$ | CH | 1·5662 | 4 | 5 | 5 | 5 | 5 | 5 | 7·23 | 0·56 |
| **12n** | 3-$C_2H_5$ | CH | 61–64°C | 1 | 4 | 3 | 5 | 4 | 3 | 7·11 | 1·02 |
| **12o** | 3-*t*-$C_4H_9$ | CH | 1·5680 | 2 | 3 | 2 | 4 | 4 | 0 | 6·58 | 1·98 |
| **12p** | 3-$CO_2C_2H_5$ | CH | 1·5959 | 0 | 0 | 0 | 2 | 0 | 0 | 6·77 | 0·51 |
| **12q** | 3-$CONHC_2H_5$ | CH | 1·5662 | 1 | 1 | 1 | 1 | 1 | 1 | * | |
| **12r** | 3-$CON(CH_3)_2$ | CH | 61–64°C | 0 | 0 | 1 | 1 | 1 | 0 | 5·03 | −1·51 |
| **12s** | 3-OPh | CH | 1·5680 | 0 | 0 | 1 | 1 | 1 | 0 | 6·66 | 2·08 |
| **9d** | 2,3-$Cl_2$ | N | 139–142°C | 0 | 0 | 2 | 5 | 1 | 0 | * | |
| **12t** | 2,4-$Cl_2$ | CH | 1·5965 | 3 | 2 | 5 | 5 | 5 | 1 | * | |
| **9e** | 2,5-$Cl_2$ | N | 1·5869 | 0 | 0 | 2 | 1 | 0 | 0 | * | |
| **9f** | 3,4-$Cl_2$ | N | 120–122°C | 0 | 3 | 5 | 5 | 5 | 1 | * | |
| **9g** | 3,5-$Cl_2$ | N | 129–130°C | 0 | 0 | 0 | 0 | 0 | 0 | * | |
| **9h** | 2-Cl, 5-$CH_3$ | N | 99–102°C | 1 | 1 | 3 | 5 | 3 | 0 | * | |
| **9i** | 3-Cl, 4-$CH_3$ | N | 82–84°C | 2 | 4 | 3 | 5 | 5 | 0 | * | |

[a,b,c,d] As in Tables 1 and 2.

**TABLE 4**

Structures, Physical Properties and Post-emergence Herbicidal Activities of Phenoxyphenoxypyrimidines and Related Structures



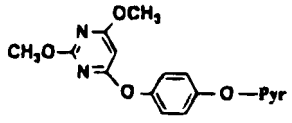
| No. | $R_3$ | X | Y | m.p. or $N_D^{20}$ | Herbicidal activity[a,b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ech | Dig | Pol | Ama | Che | Cyp |
| **12d** | $CF_3$ | O | O | 1·5350 | 5 | 5 | 5 | 5 | 5 | 5 |
| **28** | $CF_3$ | —[c] | O | 71–74°C | 0 | 0 | 0 | 0 | 0 | 0 |
| **31** | $CF_3$ | $CH_2O$ | O | 1·5482 | 0 | 0 | 1 | 1 | 0 | 0 |
| **36** | $CF_3$ | $CH_2$ | O | 1·5471 | 5 | 5 | 5 | 5 | 5 | 5 |
| **37** | $CF_3$ | $CH(CH_3)$ | O | 1·5320 | 0 | 0 | 1 | 0 | 1 | 0 |
| **12i** | H | O | O | 1·5759 | 4 | 4 | 5 | 5 | 4 | 4 |
| **12u** | H | O | —[d] | 81–82°C | 0 | 0 | 1 | 0 | 0 | 0 |
| **12v** | $CF_3$ | O | $OCH_2$ | 89–91°C | 0 | 2 | 2 | 3 | 2 | 0 |
| **12w** | H | O | $CH_2$ | 63–65°C | 2 | 3 | 4 | 5 | 4 | 2 |
| **12x** | H | O | $C(CH_3)_2$ | 1·5660 | 0 | 0 | 0 | 0 | 0 | 0 |
| **12y** | $CF_3$ | O | NH | 85–87°C | 0 | 1 | 2 | 2 | 2 | 1 |

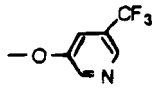
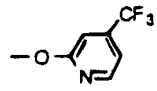
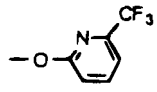
[a,b] As in Table 1.

[c] 2,4-Dimethoxy-6-[4-(3-trifluoromethylphenoxy)phenyl]pyrimidine.

[d] 2,4-Dimethoxy-6-[4-(3-trifluoromethylphenyl)phenoxyl]pyrimidine.

**TABLE 5**
Structures, Physical Properties and Post-emergence Herbicidal Activities of Pyridinoxyphenoxypyrimidines



| No. | -Pyr. | m.p. or $n_D^{20}$ | Herbicidal activity[a,b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Ech | Dig | Pol | Ama | Che | Cyp |
| **12'a** |  | 121 123°C | 0 | 0 | 0 | 0 | 0 | 0 |
| **12'b** |  | 98–100°C | 1 | 3 | 5 | 5 | 5 | 1 |
| **12'c** |  | 1·5380 | 3 | 4 | 5 | 5 | 5 | 3 |

[a,b] As in Table 1.

corn (*Zea mays* L.), soybean (*Glycine max* (L.) Merr.), cotton (*Gossypium hirsutum* L.), velvetleaf (*Abutilon theophrasti* (L.) Medic.) and common cocklebur (*Xanthium strumarium* L.). The herbicidal activities presented in Table 6 for crops and weeds are the injury ratings for the 11 species tested at 0·25 and 0·5 kg AI $ha^{-1}$. Atrazine, a reference herbicide, was also applied in a wettable powder formulation at the same dose.

*2.3.2 Hill reaction assay*

The chloroplasts were isolated from washed leaves of pea (*Pisum sativum*, L. cv. 'Akabanatsurunashi'). Following the procedure of Trebst,[7] the rate of reduction of 2,6-dichlorophenolindophenol (DCIP) was determined as the rate of decrease in absorption at 610 nm. The Hill inhibitory activity is expressed as $pI_{50}$, where $I_{50}$ is the molar concentration required to decrease the rate of DCIP reduction by 50% from the control value and $pI_{50}$ is the logarithm of the reciprocal $I_{50}$. The test results obtained are shown in Tables 2 and 3.

## 3 RESULTS AND DISCUSSION

From the structure of the lead compound **3a** incorporating the diphenyl ether substructure, its herbicidal activity might be expected to belong to that of the

**TABLE 6**
Post-emergence Herbicidal Activity of Leading Compounds at 0·5 and 0·25 kg AI $ha^{-1}$ on Crops and Weeds

| No. | Application rate (kg AI $ha^{-1}$) | Post-emergence herbicidal activity | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Crops[a] | | | | | Weeds[a] | | | | | |
| | | Or | Tr | Ze | Cl | Go | Ech | Dig | Pol | Abu | Xan | Cyp |
| **12d** | 0·5 | 4 | 4 | 5 | 3 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| | 0·25 | 3 | 4 | 5 | 3 | 5 | 3 | 4 | 5 | 4 | 4 | 3 |
| **9d** | 0·5 | 3 | 3 | 4 | 2 | 4 | 4 | 5 | 5 | 4 | 3 | 4 |
| | 0·25 | 2 | 2 | 3 | 1 | 3 | 3 | 4 | 5 | 3 | 2 | 3 |
| **36** | 0·5 | 4 | 4 | 5 | 3 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | 0·25 | 3 | 3 | 4 | 3 | 4 | 4 | 4 | 5 | 5 | 4 | 5 |
| Atrazine | 0·5 | 5 | 5 | 0 | 5 | 5 | 4 | 3 | 5 | 5 | 5 | 5 |
| | 0·25 | 4 | 5 | 0 | 5 | 5 | 3 | 2 | 5 | 4 | 4 | 4 |

[a] Or: *Oryza sativa*; Tr: *Triticum aestivum*; Ze: *Zea mays*; Gl: *Glycin max*; Go: *Gossypium hirsutum*; Ech: *Echinochloa crus-galli*; Dig: *Digitaria adscendens*; Pol: *Polygonum nodosum*; Abu: *Abutilon theophrasti*; Xan: *Xanthium strumarium*; Cyp: *Cyperus iria.*

diphenyl ether type. However, the herbicidal symptoms observed after treatment were yellowing with cessation of growth followed by necrosis, similar to those exhibited by the sulfonylureas (**1**).

The triazines and the pyrimidines with a phenoxyphenoxy group prepared from 2-aminotriazines and 2-aminopyrimidines were not appreciably active except for the lead compound **3a** and its methanesulfonyl analogue **3b** as shown in Table 1.

The herbicidal spectrum of the 2,4-dimethoxy compound **9a** was broader than that of the lead compound **3a**. Plants treated with compound **9a** showed leaf chlorosis and burned-tip symptoms three days after the spray. Susceptible species died seven days later. Symptoms were not similar to those of the lead compound **3a** but rather to those caused by Hill reaction inhibitors. To develop more active herbicides, we also tried to make structural modifications to compound **9a**.

### 3.1 The effects of replacement of the nitrogen-heterocyclic moiety

As shown in Table 2, the pyrimidine **12d** and the triazine **9b** exhibited good herbicidal activity, whereas the pyridine **25** was less active and had a narrower spectrum at the rate of 1 kg AI $ha^{-1}$. The position of the phenoxyphenoxy moiety on the pyrimidine ring was important for activity. Thus, substitution at the 6-position was favourable, as in compound **12d**, whereas the 2-substituted isomer **17** showed no activity. The results suggest that the herbicidal activity is related to the activity of Hill reaction inhibition ($pI_{50}$).

### 3.2 Substitution patterns on the pyrimidine and triazine rings

As shown in Table 2, various pairs of substituents such as lower alkyl, alkoxy, alkylthio and alkylamino were introduced into 2- and 4-positions on the pyrimidine and triazine rings. The 2,4-dimethoxy substituted pyrimidine **12d** and triazine **9b** were the most effective compounds.

### 3.3 Substitution patterns in the phenoxyphenoxy substructure

*3.3.1 Substitution patterns on the terminal phenyl ring*

As shown in Table 3, the $R_3$ substituent position was found to be critical in determining the activity. While the 2-$CF_3$ substituted compound **9c** was inactive, its isomers, especially, the 3-$CF_3$ compounds **12d** and **9d** had good activity, as did the unsubstituted compound **12i**, 3-halo compounds **12j**, **12k**, **12l** and the 3-methyl compound **12m**. In contrast, 3-esters **12p** and amides (**12q**, **12r**) had very weak activity.

*3.3.2 The effect of substituents of the terminal phenyl ring on inhibition of the Hill reaction*

The $pI_{50}$ values for some of the compounds were measured using pea chloroplast as shown in Tables 2 and 3. For a set of dimethoxypyrimidine compounds having various 3-substituents on the terminal phenyl ring in Table 3, the relationship between the $pI_{50}$ value and hydrophobicity parameter $\pi$ for $R_3$ substituents was analyzed quantitatively with eqn (1) showing a good correlation. Furthermore, the addition of $\sigma m$ to eqn (1) did not improve the correlation.

$$pI_{50} = \underset{(0\cdot09)}{-0\cdot39\pi^2} + \underset{(0\cdot14)}{0\cdot65\pi} + \underset{(0\cdot16)}{6\cdot91}$$
$$n = 11, \quad s = 0\cdot17, \quad r = 0\cdot97 \qquad (1)$$

In this equation, $n$ is the number of compounds included in the correlation, $s$ is the standard deviation, and $r$ is the correlation coefficient. The figures in parentheses under each coefficient are the 95% confidence intervals of the regression coefficient. The constant $\pi$ used in eqn (1) was that derived from a substituted phenoxyacetic acid series.[8] Equation (1) indicates that a parabolic relationship exists between the activity and the hydrophobic parameter $\pi$ for the set of 2,4-dimethoxypyrimidines.

*3.3.3 The effect of variations in the bridge linking aromatic rings*

As shown in Table 4, the methylene and ether bridges are interchangeable without significant loss of the activity for the connection of the heteroaromatic and central benzene rings (compounds **12d** and **36**) as well as the two benzene rings (compounds **12i** and **12w**). Compounds **31** and **12v** with a bond longer than methylene and compounds **37** and **12x** with a branched alkylene bridges were inactive or slightly active. Compounds **28** and **12u** with a direct link between two rings were inactive.

*3.3.4 The terminal phenyl ring structure*

As shown in Table 5, the activity of the compounds **12'a**–**12'c** in which the terminal phenyl ring is replaced by pyridine depends on the position of attachment to the pyridine ring. Thus, the pyridin-2-yl compounds **12'b** and **12'c** were active, whereas the pyridin-3-yl isomer **12'a** was inactive.

### 3.4 Herbicidal activity at lower doses

To examine selectivity against crops together with herbicidal activity against weeds, the most active compounds **12d**, **9b** and **36** were tested at lower doses as shown in Table 6. These three compounds showed good activity at 0·25 kg AI $ha^{-1}$ against most of the weeds, the pyrimidines **12d** and **36** being slightly more active

than the triazine **9b**. Unfortunately all three of these compounds were very phytotoxic to crops such as soybean, corn, rice and wheat, thus precluding their use in the field. Compounds **9f**, **12f**, **12i**, **12j**, **12k**, **12m**, **12t**, **21d**, **12'b** and **12'c** were only weakly active at 0·25 kg AI $ha^{-1}$.

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